PB90-142399

# Health Effects Assessment for Cadmium

(U.S.) Environmental Protection Agency, Cincinnati, OH

Aug 88

U.S. Department of Commerce
National Technical Information Service
NTIS

PB90-142399
EPA/600/8-89/087
August, 1988

# HEALTH EFFECTS ASSESSMENT FOR CADMIUM

ENVIRONMENTAL CRITERIA AND ASSESSMENT OFFICE
OFFICE OF HEALTH AND ENVIRONMENTAL ASSESSMENT
OFFICE OF RESEARCH AND DEVELOPMENT
U.S. ENVIRONMENTAL PROTECTION AGENCY
CINCINNATI, OH 45268

REPRODUCED BY
U.S. DEPARTMENT OF COMMERCE
NATIONAL TECHNICAL INFORMATION SERVICE
SPRINGFIELD, VA. 22161

| TECHNICAL REPORT DATA (Please read instructions on the reverse before completing) | | |
|---|---|---|
| 1. REPORT NO. EPA/600/8-89/087 | 2. | 3. RECIPIENT'S ACCESSION NO PB90 142399/AS |
| 4. TITLE AND SUBTITLE Updated Health Effects Assessment for Cadmium | | 5. REPORT DATE<br>6. PERFORMING ORGANIZATION CODE |
| 7. AUTHOR(S) | | 8. PERFORMING ORGANIZATION REPORT NO |
| 9. PERFORMING ORGANIZATION NAME AND ADDRESS | | 10. PROGRAM ELEMENT NO<br>11. CONTRACT/GRANT NO |
| 12. SPONSORING AGENCY NAME AND ADDRESS Environmental Criteria and Assessment Office<br>Office of Research and Development<br>U.S. Environmental Protection Agency<br>Cincinnati, OH 45268 | | 13. TYPE OF REPORT AND PERIOD COVERED<br>14. SPONSORING AGENCY CODE EPA/600/22 |
| 15. SUPPLEMENTARY NOTES | | |

16. ABSTRACT

This report summarizes and evaluates information relevant to a preliminary interim assessment of adverse health effects associated with specific chemicals or compounds. The Office of Emergency and Remedial Response (Superfund) uses these documents in preparing cost-benefit analyses under Executive Order 12991 for decision-making under CERCLA. All estimates of acceptable intakes and carcinogenic potency presented in this document should be considered as preliminary and reflect limited resources allocated to this project. The intent in these assessments is to suggest acceptable exposure levels whenever sufficient data are available. The interim values presented reflect the relative degree of hazard associated with exposure or risk to the chemical(s) addressed. Whenever possible, two categories of values have been estimated for systemic toxicants (toxicants for which cancer is not the endpoint of concern). The first, $RfD_S$ or subchronic reference dose, is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs during a limited time interval. The RfD is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs for a significant portion of the lifespan. For compounds for which there is sufficient evidence of carcinogenicity, $q_1^*$s have been computed, if appropriate, based on oral and inhalation data if available.

| 17. KEY WORDS AND DOCUMENT ANALYSIS | | |
|---|---|---|
| a. DESCRIPTORS | b. IDENTIFIERS/OPEN ENDED TERMS | c. COSATI Field/Group |
| | | |
| 18. DISTRIBUTION STATEMENT Public | 19. SECURITY CLASS (This Report) Unclassified | 21. NO. OF PAGES 59 |
| | 20. SECURITY CLASS (This page) Unclassified | 22. PRICE |

EPA Form 2220-1 (Rev. 4-77) PREVIOUS EDITION IS OBSOLETE

## DISCLAIMER

This document has been reviewed in accordance with the U.S. Environmental Protection Agency's peer and administrative review policies and approved for publication. Mention of trade names or commercial products does not constitute endorsement or recommendation for use.

## PREFACE

This report summarizes and evaluates information relevant to a preliminary interim assessment of adverse health effects associated with cadmium. All estimates of acceptable intakes and carcinogenic potency presented in this document should be considered as preliminary and reflect limited resources allocated to this project. Pertinent toxicologic and environmental data were located through on-line literature searches of the TOXLINE, CANCERLINE and the CHEMFATE/DATALOG data bases. The basic literature searched supporting this document is current up to May, 1987. Secondary sources of information have also been relied upon in the preparation of this report and represent large-scale health assessment efforts that entail extensive peer and Agency review. The following Office of Health and Environmental Assessment (OHEA) sources have been extensively utilized:

U.S. EPA. 1980a. Ambient Water Quality Criteria for Cadmium. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Water Regulations and Standards, Washington, DC. EPA 440/5-80-025. NTIS PB 81-117368.

U.S. EPA. 1982. Review of Toxicologic Data in Support of Evaluation for Carcinogenic Potential of Cadmium and Compounds. Prepared by the Office of Health and Environmental Assessment, Carcinogen Assessment Group, Washington, DC for the Office of Solid Waste and Emergency Response, Washington, DC.

U.S. EPA. 1983. Reportable Quantity for Cadmium (and Compounds). Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste and Emergency Response, Washington, DC.

U.S. EPA. 1985a. Updated mutagenicity and carcinogenicity assessment of cadmium. Prepared by the Office of Health and Environmental Assessment, Carcinogen Assessment Group, Washington, DC. NTIS PB 85-243533.

The intent in these assessments is to suggest acceptable exposure levels for noncarcinogens and risk cancer potency estimates for carcinogens whenever sufficient data were available. Values were not derived nor were larger uncertainty factors employed when the variable data were limited in scope tending to generate conservative (i.e., protective) estimates. Nevertheless, the interim values presented reflect the relative degree of hazard or risk associated with exposure to the chemical(s) addressed.

Whenever possible, two categories of values have been estimated for systemic toxicants (toxicants for which cancer is not the endpoint of concern). The first, $RfD_S$ (formerly AIS) or subchronic reference dose, is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs during a limited time interval (i.e., for an interval that does not constitute a significant portion of the lifespan).

This type of exposure estimate has not been extensively used, or rigorously defined, as previous risk assessment efforts have been primarily directed towards exposures from toxicants in ambient air or water where lifetime exposure is assumed. Animal data used for $RfD_S$ estimates generally include exposures with durations of 30-90 days. Subchronic human data are rarely available. Reported exposures are usually from chronic occupational exposure situations or from reports of acute accidental exposure. These values are developed for both inhalation ($RfD_{SI}$) and oral ($RfD_{SO}$) exposures.

The RfD (formerly AIC) is similar in concept and addresses chronic exposure. It is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs for a significant portion of the lifespan [see U.S. EPA (1980b) for a discussion of this concept]. The RfD is route-specific and estimates acceptable exposure for either oral ($RfD_O$) or inhalation ($RfD_I$) with the implicit assumption that exposure by other routes is insignificant.

Composite scores (CSs) for noncarcinogens have also been calculated where data permitted. These values are used for identifying reportable quantities and the methodology for their development is explained in U.S. EPA (1984).

For compounds for which there is sufficient evidence of carcinogenicity $RfD_S$ and RfD values are not derived. For a discussion of risk assessment methodology for carcinogens refer to U.S. EPA (1980b). Since cancer is a process that is not characterized by a threshold, <u>any</u> exposure contributes an increment of risk. For carcinogens, $q_1^*$s have been computed, if appropriate, based on oral and inhalation data if available.

## ABSTRACT

In order to place the risk assessment evaluation in proper context, refer to the preface of this document. The preface outlines limitations applicable to all documents of th4s series as well as the appropriate interpretation and use of the quantitative estimates presented.

A dose-related increase in lung cancer has been reported in rats exposed to cadmium chloride aerosols. U.S. EPA (1985a) based cancer risk assessment on the maximum likelihood estimate of unit risk of $1.8 \times 10^{-3}$ for 1 $\mu g/m^3$ in air, based on an epidemiologic study associating occupational exposure with lung cancer. This unit risk corresponds to a unit risk slope of 6.1 $(mg/kg/day)^{-1}$. This value was verified by the CRAVE Workgroup (U.S. EPA, 1988a).

Cancer induction has not been shown in animal studies by the oral route (possibly due to poor absorption). U.S. EPA (1988b) calculated an RfD for oral exposure to cadmium based on the generally accepted critical level of cadmium in the renal cortex, 200 $\mu g/g$, which is associated with abnormal kidney function in humans. A pharmacokinetic model was used to calculate a daily oral dose that would produce this level in a chronic exposure situation. The resulting RfD was 0.04 mg/day or 0.0005 mg/kg/day for a 70 kg adult for waterborne exposures. In addition, U.S. EPA (1988b) calculated an RfD of 0.001 mg/kg/day for dietary exposures by reducing the assumed absorption factor.

## ACKNOWLEDGEMENTS

The initial draft of this report was prepared by Syracuse Research Corporation for EPA's Environmental Criteria and Assessment Office, Cincinnati, OH. Dr. Christopher DeRosa and Karen Blackburn were the Technical Project Monitors and Helen Ball was the Project Officer. The final documents in this series were prepared for the Office of Emergency and Remedial Response, Washington, DC.

Scientists from the following U.S. EPA offices provided review comments for this document series:

Environmental Criteria and Assessment Office, Cincinnati, OH
Carcinogen Assessment Group
Office of Air Quality Planning and Standards
Office of Solid Waste
Office of Toxic Substances
Office of Drinking Water
Office of Pesticide Programs

Editorial review for the document series was provided by the following:

Judith Olsen and Erma Durden
Environmental Criteria and Assessment Office
Cincinnati, OH

Technical support services for the document series was provided by the following:

Bette Zwayer, Pat Daunt, Karen Mann and Jacky Bohanon
Environmental Criteria and Assessment Office
Cincinnati, OH

TABLE OF CONTENTS


| | | Page |
|---|---|---|
| 1. | ENVIRONMENTAL CHEMISTRY AND FATE | 1 |
| 2. | ABSORPTION FACTORS IN HUMANS AND EXPERIMENTAL ANIMALS | 3 |
| | 2.1. ORAL | 3 |
| | 2.2. INHALATION | 4 |
| 3. | TOXICITY IN HUMANS AND EXPERIMENTAL ANIMALS | 5 |
| | 3.1. SUBCHRONIC | 5 |
| | 3.1.1. Oral | 5 |
| | 3.1.2. Inhalation | 7 |
| | 3.2. CHRONIC | 7 |
| | 3.2.1. Oral | 7 |
| | 3.2.2. Inhalation | 9 |
| | 3.3. TERATOGENICITY AND OTHER REPRODUCTIVE EFFECTS | 12 |
| | 3.3.1. Oral | 12 |
| | 3.3.2. Inhalation | 12 |
| | 3.4. TOXICANT INTERACTIONS | 12 |
| 4. | CARCINOGENICITY | 14 |
| | 4.1. HUMAN DATA | 14 |
| | 4.1.1. Oral | 14 |
| | 4.1.2. Inhalation | 14 |
| | 4.2. BIOASSAYS | 16 |
| | 4.2.1. Oral | 16 |
| | 4.2.2. Inhalation | 17 |
| | 4.3. OTHER RELEVANT DATA | 18 |
| | 4.4. WEIGHT OF EVIDENCE | 18 |
| 5. | REGULATORY STANDARDS AND CRITERIA | 25 |
| 6. | RISK ASSESSMENT | 27 |
| | 6.1. REFERENCE DOSE SUBCHRONIC ($RfD_S$) | 27 |
| | 6.1.1. Oral ($RfD_{SO}$) | 27 |
| | 6.1.2. Inhalation ($RfD_{SI}$) | 27 |

TABLE OF CONTENTS


| | Page |
|---|---|
| 6.2. REFERENCE DOSE (RfD) | 27 |
| 6.2.1. Oral ($RfD_O$) | 27 |
| 6.2.2. Inhalation ($RfD_I$) | 28 |
| 6.3. CARCINOGENIC POTENCY ($q_1^*$) | 28 |
| 6.3.1. Oral | 28 |
| 6.3.2. Inhalation | 29 |
| 7. REFERENCES | 31 |
| APPENDIX: Summary Table for Cadmium | 48 |

## LIST OF TABLES


| No. | Title | Page |
|---|---|---|
| 3-1 | Subchronic Oral Toxicity of Cadmium . . . . . | 6 |
| 3-2 | Chronic Oral Toxicity of Cadmium. . . . . | 8 |
| 3-3 | Chronic Inhalation Toxicity of Cadmium from Occupational Exposure. . . . . | 10 |
| 4-1 | Epidemiology of Cadmium-associated Respiratory Cancer . . . . | 15 |
| 4-2 | Mutagenicity of Cadmium: Evaluations Using Prokaryotes. . . . | 19 |
| 4-3 | Mutagenicity of Cadmium: Evaluations Using Eukaryotic Cells . . . . . | 20 |
| 4-4 | Mutagenicity of Cadmium: Evaluations Using Insects. . . . . | 21 |
| 4-5 | Mutagenicity of Cadmium: *In vitro* Chromosome Aberrations. . . | 22 |
| 4-6 | Mutagenicity of Cadmium: *In vivo* Mammalian Systems. . . . . | 23 |

## LIST OF ABBREVIATIONS

| | |
|---|---|
| BCF | Bioconcentration factor |
| bw | Body weight |
| CAS | Chemical Abstract Service |
| CS | Composite score |
| DMSO | Dimethyl sulfoxide |
| DNA | Deoxyribonucleic acid |
| HA | Health advisory |
| LOEL | Lowest-observed-effect level |
| NOAEL | No-observed-adverse-effect level |
| PEL | Permissible exposure limit |
| RfD | Reference dose |
| $RfD_I$ | Inhalation reference dose |
| $RfD_O$ | Oral reference dose |
| $RfD_S$ | Subchronic reference dose |
| $RfD_{SI}$ | Subchronic inhalation reference dose |
| $RfD_{SO}$ | Subchronic oral reference dose |
| SNARL | Suggested no adverse response level |
| STEL | Short-term exposure limit |
| TLV | Threshold limit value |
| TWA | Time-weighted average |

# 1. ENVIRONMENTAL CHEMISTRY AND FATE

Cadmium is a metal belonging to Group IIB of the Periodic Table. Elemental cadmium has a CAS Registry number of 7440-43-9. It occurs in the environment in the zero valence (metal and alloys) and in the +2 valence (compound) states. Besides forming simple ionic and covalent compounds with anions and groups, cadmium also forms complexes with ammonia, cyanide, halides and thiocyanate (Hollander and Carapella, 1978). Several of the inorganic cadmium compounds are quite soluble in water (for example, chloride and sulfate). Cadmium oxide and sulfide are almost insoluble in water (Weast, 1985).

In the atmosphere cadmium is expected to be present as dust and fumes from smelting of ores, manufacturing and reprocessing of alloys, recycling of steel scrap, emissions of coal-fired power plants and incineration of solid wastes (Fishbein, 1981). The atmospheric fate of cadmium has not been studied comprehensively. Any chemical interaction of cadmium compounds in the atmosphere is likely to result in speciation (for example, conversion into a more stable species such as CdO), and not in its direct removal through decomposition, as frequently occurs with organic compounds. The principal removal mechanism for atmospheric cadmium may be wet and dry deposition (Fishbein, 1981). The atmospheric half-life for the physical removal mechanism is expected to depend on the particle size and particle density of atmospheric cadmium. There is considerable evidence that cadmium is concentrated in smaller (<3 μm) particles in the atmosphere (Fishbein, 1981). Therefore, it may have a long half-life in the atmosphere, although no estimate for this half-life is available.

The dominant fate of cadmium in aquatic media is sedimentation through sorption onto iron oxides, magnesium oxides or organic matter; coprecipitation with hydrous iron, aluminum and manganese oxides; and isomorphous substitution in carbonate minerals. Smaller amounts of cadmium may persist in the aquatic phase in solution, either as hydrated cations or as organic or inorganic complexes (Davies-Colley et al., 1984; Callahan et al., 1979).

In most unpolluted water, the majority of soluble cadmium may be present as the hydrated cation; whereas, in polluted water, complexation with organic material may be most important (Callahan et al., 1979). Under anaerobic conditions, sediments may commonly act as a sink for cadmium in the form of its bisulfide or polysulfide (Davies-Colley et al., 1985).

BCFs for cadmium in aquatic organisms have been determined by a number of investigators. In freshwater and marine fish, BCFs vary between 1000 and 3000 (Callahan et al., 1979). These BCF values suggest that bioaccumulation in aquatic organisms would be significant.

The fate of cadmium in soil is complicated, depending upon soil characteristics and the concentrations of a large number of organic and inorganic species. The two major mobile forms of cadmium in soils are soluble ionic forms and complexed (with organic and inorganic ligands) forms. Both the free ions and the complexed species are subject to ion exchange, nonspecific adsorption, precipitation and surface complexation (Gerritse and Van Driel, 1984). In general, cadmium is expected to adsorb strongly to soil with sorption increasing as the organic content of the soil increases (Elliot et al., 1986). Conditions that may weaken the adsorption process in soil (i.e., acidic conditions or increased salinity) may enhance desorption from soil and lead to increased mobility. For near neutral and alkaline soils, precipitation and complexation reactions will be more important than adsorption (Elliot et al., 1986).

## 2. ABSORPTION FACTORS IN HUMANS AND EXPERIMENTAL ANIMALS

### 2.1. ORAL

Several studies indicate that cadmium is poorly absorbed following oral administration. Friberg et al. (1974) reported that ~2% of orally administered cadmium was absorbed by experimental animals (species and compound not specified in the review). Stokinger (1981) reported that 88% of an oral dose of cadmium administered to rats was excreted in the feces. About 1% of the dose was located in the liver and the kidneys. These data suggest a maximum for gastrointestinal absorption of ~12%. More recently, Andersen et al. (1986) administered $^{109}Cd$ in water to male CBA mice by stomach tube and determined elimination and body retention in a gamma counter. Doses ranged from 140-790 μmol/kg (~16-89 mg/kg). Gastrointestinal absorption was estimated as residual body burden after the rapid (elimination) phase and ranged from 1.4-4.2%. Absorption increased with increasing dose because of cadmium-induced constipation, which increased gut passage time. Absorption appears to be slightly more extensive in humans, with reported absorption values of 6 and 4.6% (Rahola et al., 1973; McLellan et al., 1978).

The absorption of orally administered cadmium may be altered by a variety of dietary parameters (Bremner, 1974). Washko and Cousins (1976) found that diets low in calcium result in a significant increase in cadmium absorption. Diets deficient in vitamin D, protein, zinc, iron and copper also increase the extent of cadmium absorption (Worker and Migicovsky, 1961; Suzuki et al., 1969; Banis et al., 1969; Bunn and Matrone, 1966; Hill et al., 1963). Ascorbic acid deficiency has been observed to increase cadmium toxicity (Fox and Fry, 1970).

## 2.2. INHALATION

Absorption of cadmium from the respiratory tract appears to be much more extensive than absorption from the gastrointestinal tract. Up to 25% of inhaled cadmium dust and aerosols may be absorbed when a large proportion of the particles are in the respirable range and the compound is relatively soluble (U.S. EPA, 1980a). Lewis et al. (1977) exposed rats, guinea pigs and cynomolgus monkeys to cadmium fumes at a TWA of 1 mg/m³ for 3-6 months before sacrifice. Based on estimations of inhaled doses, the investigators determined that rats and guinea pigs retained 11 and 36% of the dose after 3 months and monkeys retained 35% of the dose after 6 months. Up to 50% of the cadmium in cadmium fumes or cigarette smoke may be absorbed (WHO Task Group, 1977; Elinder et al., 1976).

## 3. TOXICITY IN HUMANS AND EXPERIMENTAL ANIMALS

The major effects of long-term exposure to cadmium are similar following both oral and inhalation exposure. Renal dysfunction, which results in disturbances in mineral metabolism and (eventually) formation of kidney stones or osteomalacia, is the major effect in humans. Pulmonary dysfunction is observed following higher inhalation exposures. Cadmium exposure has been correlated with hypertension in humans.

### 3.1. SUBCHRONIC

3.1.1. Oral. Subchronic oral toxicity data for cadmium are summarized in Table 3-1.

No data were located on the subchronic oral exposure of humans to cadmium.

Yuhas et al. (1979) administered cadmium acetate (0, 1, 10 or 100 mg Cd/ℓ) in the drinking water to male Sprague-Dawley rats for 13 weeks. The reported doses are not consistent with the reported water concentration, water consumption and body weights. Based on the data reported, the correct doses appear to be 0, 0.118, 0.947 and 8.041 mg/kg bw/day. At the high dose level, weight gain was depressed, the cadmium content of bone was increased, the zinc content of bone was decreased and serum phosphorus concentrations were elevated. At a dose of 0.947 mg/kg bw/day, cadmium content of bone was increased. Serum alkaline phosphatase levels was increased in all dose groups and serum phosphorus was elevated in the 100 ppm cadmium group. No histological effects were observed in any dose group. In a dietary study, 6.75 mg/kg bw/day was associated with mortality and 2.25 mg/kg bw/day was associated with anemia (Fitzhugh and Meiller, 1941).

TABLE 3-1

Subchronic Oral Toxicity of Cadmium

| Compound | Species/ Strain/Sex | Dose | Length of Exposure | Effects | Reference |
|---|---|---|---|---|---|
| Cadmium acetate | rats/Sprague-Dawley/M | 0, 1, 10 or 100 mg Cd/ℓ drinking water (0.118, 0.947 or 8.041 mg/kg bw/day) | 13 weeks | Decreased weight gain at 100 mg/ℓ; no effect on cellular structure of liver, kidney or duodenum at any dose; increased serum alkaline phosphatase in all dose groups; increased cadmium content in bone at 10 and 100 mg Cd/ℓ $H_2O$; decreased zinc content of bone at 100 mg/ℓ. | Yuhas et al., 1979 |
| Cadmium | rats/NR/NR | 0, 15, 45, 75 or 135 mg/kg diet (0, 0.75, 2.25, 3.75 or 6.75 mg/kg bw/day)* | 6 months | Marked anemia, decreased weight gain and increased mortality at 135 mg/kg diet; anemia at doses of 45 and 75 mg/kg diet | Fitzhugh and Meiller, 1941 |
| Cadmium chloride | mice/Swiss Webster/NR | 3 or 300 mg Cd/ℓ $H_2O$ (0.57 or 57 mg/kg bw/day) | 70 days | Decrease in the number of lymphocytes secreting antibodies to sheep red blood cells at both dose levels; necrosis of renal epithelial cells in the proximal convoluted tubules and collecting tubules at both doses | Koller et al., 1975 |

*Estimated using a food factor for rats of 0.05 (U.S. EPA, 1986a).

NR = Not reported



0038H
02/24/88

Koller et al. (1975) administered drinking water containing 3 or 300 mg Cd/ℓ to Swiss Webster mice (390 mice/group) for 70 days. The controls consisted of 80 mice that received deionized water. Mice were immunized with sheep red blood cells during treatment or 1, 7, 14 or 42 days after the end of treatment. The number of lymphocytes secreting antibodies to sheep red blood cells was markedly decreased in both dose groups. There was a dose-related incidence of necrosis of the renal epithelial cells in the proximal convoluted tubules and collecting tubules. Assuming that mice drink 0.0057 ℓ water/day and weigh 0.03 kg (U.S. EPA, 1986a), 3 mg/ℓ corresponds to a dose of 0.57 mg/kg bw/day.

3.1.2. Inhalation. The only subchronic inhalation study available was that of Kolakowski et al. (1983), who exposed rats to cadmium oxide fumes at concentrations of 0.16 or 1 mg Cd/m³, 5 hours/day, 5 days/week for 3-6 months. Rats were examined for effects on cardiac muscle ultrastructure. Treated rats experienced alterations of intercalated disc structure that were dependent on the level and length of exposure.

3.2. CHRONIC

3.2.1. Oral. Chronic oral toxicity data for cadmium are summarized in Table 3-2.

Schroeder et al. (1963, 1964, 1965) administered cadmium acetate in the drinking water (5 mg Cd/ℓ) to Long-Evans rats and Charles River mice for their lifetimes. Survival was decreased in both sexes of rats and in male mice. In rats, treatment was associated with renal and cardiac arteriosclerosis, cardiac hypertrophy and neurological effects. The major effect reported in mice was altered renal morphology. Renal degeneration and necrosis have also been reported in Wistar rats given 123 mg Cd (from cadmium chloride)/ℓ drinking water (Kajikawa et al., 1981).

TABLE 3-2

Chronic Oral Toxicity of Cadmium

| Compound | Species/ Strain/Sex | Dose | Length of Exposure | Effects | Reference |
|---|---|---|---|---|---|
| Cadmium acetate | rats/Long-Evans/M,F | 0 or 5 mg Cd/ℓ $H_2O$ | lifetime (~2.5 years) | Decreased survival; systolic hypertension; renal and cardiac arteriosclerosis and cardiac hypertrophy; severe vestibular disturbances | Schroeder et al., 1963, 1964, 1965; Kanisawa and Schroeder, 1969 |
| Cadmium acetate | mice/Charles River/M,F | 0 or 5 mg Cd/ℓ $H_2O$ | lifetime (~2 years) | Decreased survival in males; hyalinized glomeruli, thickened basement membranes, and a reduction in the lumen/wall ratio in the arterioles of the kidneys | Schroeder et al., 1964; Kanisawa and Schroeder, 1969 |
| Cadmium | rats/Wistar/ NR | 0 or 123 mg Cd/ℓ $H_2O$ | 4-91 weeks | Vacuolar degeneration of the kidneys; cellular necrosis in the proximal convoluted tubules; increased urinary protein excretion | Kajikawa et al., 1981 |
| NR | human/NA/ M,F | 228 µg/day (estimated LOEL; 30 µg/day for a 70 kg man) | lifetime | Itai-itai disease; tubular proteinuria | Friberg et al., 1974; Muramatsu, 1974; Nogawa et al., 1978; U.S. EPA, 1980a |
| NR | human/NA/ M,F | 250-350 µg Cd/day (estimated LOEL) | 50 years | Renal dysfunction | Friberg et al., 1974 |

NA = Not applicable; NR = not reported

The U.S. EPA (1980a) has estimated the threshold dose for induction of proteinuria, based upon dietary intake data from areas of Japan in which itai-itai disease is prevalent. In these areas, ~85% of the daily cadmium intake is derived from rice (Muramatsu, 1974). Nogawa et al. (1978) found that the prevalence of tubular proteinuria in persons <70 years old did not exceed the prevalence in control populations until the cadmium levels in rice were >0.40-0.49 µg/g rice. The U.S. EPA (1980a) estimated a LOEL of 228 µg Cd/day, using an average value of 0.45 µg Cd/g rice. For a corresponding Western European or American population, the daily dose that would result in an equivalent mg/kg bw/day was estimated to be 301 µg Cd/day.

This LOEL is in good agreement with the estimate of 164-616 µg Cd/day determined by Friberg et al. (1974), based on the "generally accepted" critical cadmium level at which renal dysfunction occurs, 200 µg Cd/g wet weight of renal cortex. The Friberg assessment utilized a toxicokinetic model for cadmium accumulation in the renal cortex. The model assumed a body weight of 70 kg, an adult kidney weight of 300 g, an adult calorie intake of 2500 cal., gastrointestinal absorption of 4.5%, one-third of the body burden in the kidney and that the concentration in the renal cortex is 50% higher than the average kidney concentration. The range of daily intakes, from 196-616 µg/day to reach 200 µg/g wet weight in the cortex by age 50, was estimated by varying the percent excretion per day from 0-0.02, which effectively changes the biological half-life by an order of magnitude. Friberg (1984) felt that the three lowest excretion rates that corresponded to intakes of 164, 196 and 248 µg/day gave the most plausible intake figures.

3.2.2. Inhalation. Chronic inhalation toxicity data for cadmium are summarized in Table 3-3.

TABLE 3-3

Chronic Inhalation Toxicity of Cadmium from Occupational Exposure

| Compound | Dose | Length of Exposure | Effects | Reference |
|---|---|---|---|---|
| Cadmium dust (<5 μ, diameter) | 21 μg Cd/m³ (66 μg total Cd/m³) | 21-40 years | Decreased pulmonary ventilatory function; increased incidence of kidney dysfunction; increased proteinuria | Lauwerys et al., 1974 |
| Cadmium fumes | 125 μg Cd/m³ | 9 months to 12 years | Anemia; elevated urinary protein levels | Tsuchiya, 1967 |
| Cadmium iron oxide dust | NR | NR | Emphysema; proteinuria | Friberg, 1948a,b, 1950 |
| Cadmium fumes | ≤100 μg/m³ | ≥21 years | Renal dysfunction | Falck et al., 1983 |
| Various compounds of cadmium plus nickel or copper | exposure classified as "always low," "ever medium" or "ever high" | NR | Significantly increased incidence of deaths from bronchitis or emphysema in the "ever high" group, directly related to duration of exposure | Armstrong and Kazantzis, 1985 |

NR = Not reported



0038H

02/24/88

In a study of workers exposed to cadmium iron oxide dust in a Swedish alkaline battery factory, Friberg (1948a,b, 1950) observed a correlation between cadmium exposure and the development of emphysema. These findings have since been confirmed by a number of investigators (Paterson, 1947; Baader, 1952; Lane and Campbell, 1954; Buxton, 1956; Smith et al., 1960, 1976; Kazantzis et al., 1963; Potts, 1965; Holden, 1965; Lewis et al., 1969; Snider et al., 1973; Lauwerys et al., 1974). Cadmium-induced emphysema is only observed following inhalation exposure.

Tsuchiya (1967) studied 13 workers who had been exposed to cadmium fumes (TWA = 125 μg Cd/m³) for 9 months to 12 years. The control group consisted of 13 age-matched nonexposed workers. The only effects noted were decreased blood hemoglobin levels and elevated urinary protein levels.

Lauwerys et al. (1974) studied 22 male workers who were exposed to an average respirable cadmium dust (<5 μ, aerodynamic diameter) concentration of 21 μg Cd/m³ for 21-40 years. The total airborne cadmium concentration averaged 66 μg Cd/m³. The control group was matched to the exposed group by age, sex, weight, height, smoking habits and socioeconomic status. Kidney dysfunction, as indicated by proteinuria, was observed in 68% of the cadmium-exposed group as compared with 15% in the control group. Measures of pulmonary ventilatory function (forced vital capacity, forced expiratory volume/second and peak expiratory flow rate) were reduced in the cadmium-exposed group.

Falck et al. (1983) examined 33 male workers exposed to cadmium fumes at or below the current OSHA (1985) PEL of 100 μg/m³ for at least 21 years. These workers had an increased incidence of renal dysfunction compared with a control group, and this effect did not appear to be related to smoking habits or ingestion of cadmium. In British workers exposed to various

compounds of cadmium, some in addition to nickel or copper, Armstrong and Kazantzis (1985) found a positive association with increased risk of death from bronchitis or emphysema. Risk appeared to increase with duration of exposure. There was also a marginal but not statistically significant association with increased risk of death from nephritis or nephrosis in the "ever high" group.

## 3.3. TERATOGENICITY AND OTHER REPRODUCTIVE EFFECTS

3.3.1. Oral. Dixon et al. (1976) reported that a concentration of 0.1 mg cadmium/ℓ administered to rats in their drinking water for 90 days produced no detectable effects on reproduction. Schroeder and Mitchener (1971) investigated the effect of 10 mg cadmium (unspecified soluble salt)/ℓ drinking water on reproductive performance in mice. The treated mice failed to reproduce past the second generation. Nearly a third of the offspring died before weaning, and 13.3% of the survivors were classified as runts. Cadmium has also been demonstrated to be teratogenic and to reduce fertility following intravenous, intraperitoneal and subcutaneous administration (U.S. EPA, 1980a).

3.3.2. Inhalation. Pertinent data regarding the teratogenicity or other reproductive effects of inhaled cadmium were not located in the available literature.

## 3.4. TOXICANT INTERACTIONS

The absorption and toxicity of cadmium may be altered by a number of dietary factors (see Section 2.1.). In experimental animals, zinc has been reported to prevent or reduce cadmium-induced testicular damage, teratogenic effects, growth inhibition and tumor induction (Parizek, 1957; Parizek et al., 1969; Ferm and Carpenter, 1967; Gunn et al., 1963a,b, 1964). Increased dietary copper has been demonstrated to prevent or reduce cadmium-induced

mortality, anemia and degeneration of aortic elastin (Hill et al., 1963; Bunn and Matrone, 1966). Dietary cadmium inhibits intestinal absorption of copper and calcium, possibly leading to deficiencies of these elements (Starcher, 1969; Ando et al., 1977; Kobayashi, 1970).

## 4. CARCINOGENICITY

### 4.1. HUMAN DATA

4.1.1. Oral. Pertinent data regarding the oral carcinogenicity of cadmium in humans were not located in the available literature.

4.1.2. Inhalation. It is beyond the scope of this document to present all of the available epidemiologic data concerning cadmium and cancer. A summary of relevant studies was compiled by Oberdorster (1986) (Table 4-1). The Carcinogen Assessment Group (CAG) has prepared an in-depth review of the evidence available concerning the carcinogenicity of cadmium (U.S. EPA, 1985a). The conclusions drawn from this review were that the weight of the evidence suggests a significant risk of lung cancer from exposure to cadmium, that the evidence that cadmium is a potent lung carcinogen is to be considered limited, and that cadmium is classified as a B1 carcinogen.

U.S. EPA (1985a) considered that the data presented by Thun et al. (1985) provided the strongest evidence for cadmium as a causative agent in human cancer. The Thun et al. (1985) study examined a cohort of cadmium smelter workers employed for $\geq$2 years in a production capacity within one plant between January 1, 1940 and December 31, 1969. This cohort had a total of 16 deaths from respiratory cancer through December 31, 1978; 7.00 deaths from this cause would have been expected based on calendar time age-specific death rates for white males in the United States. In this study, there was a 2-fold excess risk of lung cancer in cadmium smelter workers; this was attributed to cadmium exposure and not to the confounding factors of cigarette smoking and arsenic exposure. Other studies provided supporting evidence for increased risk of lung cancer from cadmium exposure, but these studies were less well-conducted than the Thun et al. (1985) study.

TABLE 4-1

Epidemiology of Cadmium-associated Respiratory Cancer*

| Exposure | Study Group | Findings | Reference |
|---|---|---|---|
| CdO dust | 74 workers in an alkaline battery factory | One cancer of bronchus (no control group for comparison) | Potts, 1965 |
| CdO dust | 246 workers | No excess lung cancers | Kipling and Waterhouse, 1967 |
| $Cd(OH)_2$, $Ni(OH)_2$ | 536 workers in an alkaline battery factory | No excess cancer of any organ | Kuperdinck, 1968 |
| CdO (some As) | 292 cadmium smelter workers | Increased mortality from lung cancer (no correction for arsenic or smoking) | Lemen et al., 1976 |
| $Cd(OH)_2$, $Ni(OH)_2$ | 269 workers in a cadmium-nickel factory and 94 cadmium-copper alloy workers | Excess cancer of nasopharynx (concurrent exposure to nickel) | Kjellström et al., 1979 |
| CdO (fume) | 347 cadmium-copper alloy workers and 624 vicinity workers | Excess deaths from pulmonary disease (not cancer), elevated risk of lung cancer in vicinity workers (arsenic?, smoking?) | Holden, 1980 |
| CdO and $Cd(OH)_2$ dust, $Ni(OH)_2$ | 3025 nickel-cadmium battery workers | Significant increase in respiratory cancer in "highly or moderately" exposed workers but not in "high exposure" group (nickel hydroxide and welding fumes confounding factors?) | Sorahan and Waterhouse, 1983 |
| CdO dust and fume, CdS, dust from Cd stabilizers | 6995 male cadmium workers of 17 different plants | Significant excess of lung cancers in the "always low" exposure group only, probably not related to cadmium; high risk of dying from bronchitis in "ever high" exposure group | Armstrong and Kazantzis, 1983 |
| CdO dust, $Ni(OH)_2$ | 522 workers of cadmium-nickel battery factory | Insignificant increase in lung cancer (eight observed, six expected); one cancer of nasopharynx (nickel?) | Elinder et al., 1985 [update of study by Kjellström et al. (1979)] |
| CdO dust and fume, $CdSO_4$, CdS (some As) | 602 cadmium production workers | Lung cancer incidence increased significantly with cumulative exposure; smoking and arsenic exposure did not account for increase | Thun et al., 1985 [update of study by Lemen et al. (1976)] |
| CdO dust and fume, CdS, $CdSO_4$ (some As) | 672 cadmium production workers [same plant as in Thun et al. (1985) study] | No excess lung cancer from cadmium when corrected for personal smoking history and arsenic exposure | White et al., 1985 |

*Source: Oberdorster, 1986



0038H
07/18/88

U.S. EPA (1985a) points out several problems associated with using this study for risk assessment purposes:

1. Smoking rate may have been higher for this cohort as compared with the general population.
2. Exposure is confounded by exposure to arsenic, a known respiratory carcinogen.
3. Very limited characterization of exposure levels and duration.
4. No exposure estimates for individuals.
5. Available data do not allow evaluation of goodness of fit for the mathematical model(s) used in risk assessment.

Despite these reservations, U.S. EPA (1985a) felt that a risk assessment based on these data could be useful. The cancer response did correspond in terms of site to animal response. In addition, the confounding factors should increase the apparent cancer risk thus producing an upper-bound or more protective estimate.

In addition to an increased incidence of lung cancer, exposure to cadmium has been weakly associated with an increased incidence of prostatic cancer in humans (Piscator, 1981; Lemen et al., 1976; Kipling and Waterhouse, 1967). U.S. EPA (1985a) concluded that the evidence was insufficient to conclude that cadmium was a prostatic carcinogen.

## 4.2. BIOASSAYS

4.2.1. Oral. Schroeder et al. (1964) administered drinking water containing cadmium acetate (5 µg Cd/mL $H_2O$) to a group of 48 male and 39 female mice for their lifetime. Significant decreases in the incidence of pulmonary tumors and total tumor incidence were observed in the cadmium-treated animals; however, mean survival time was also reduced.

Levy et al. (1975) administered weekly doses of cadmium sulfate by gavage to groups of 50 male Swiss mice (0.44, 0.88 or 1.75 mg Cd/kg bw) for 18 months. No tumors of the prostate gland were detected.

Schroeder et al. (1965) and Kanisawa and Schroeder (1969) administered drinking water containing cadmium acetate (5 µg Cd/mL) to Long-Evans rats for their lifetime. No significant differences were observed in total tumor incidence or the incidence of any specific tumor type between treated and control groups.

Levy and Clark (1975) administered weekly doses of 0.09, 0.18 or 0.35 mg Cd/kg bw as cadmium sulfate to groups of 30 male CB hooded rats by gavage for 2 years. There was no treatment-related increase in either the total tumor incidence or the incidence of prostate tumors.

Decker et al. (1958) administered cadmium chloride (0.1, 0.5, 2.5, 5.0 or 10.0 mg Cd/L drinking water) to groups of eight male and eight female Sprague-Dawley rats for 1 year. No tumors were found that could be attributed to cadmium treatment. Loser (1980) and Sato (1977) also failed to find an association between oral administration of cadmium and the development of tumors.

4.2.2. Inhalation. Paterson (1947) reported a study in which rats were exposed to cadmium oxide and cadmium chloride fumes; however, IARC (1976) concluded that the duration of exposure was too short to draw any conclusions from the reported absence of tumors.

Takenaka et al. (1983) exposed male Wistar rats to three concentrations of cadmium chloride aerosols. Measured cadmium chloride concentrations averaged 50.8, 25.7 and 13.4 µg/m³ for the three groups, respectively. Forty rats were included in each cadmium group and 41 control rats were exposed to filtered air. Rats were exposed continuously for 18 months.

Following the treatment period rats were kept an additional 13 months and then sacrificed.

There were no significant differences between groups in terms of body weights or survival times ($p<0.05$). A dose-related increase in primary lung carcinomas was seen. Lung carcinoma incidences were 0/38, 6/39, 20/38 and 25/35 for the 0, 13.4, 25.7 and 50.8 $\mu g/m^3$ cadmium chloride groups, respectively.

## 4.3. OTHER RELEVANT DATA

The results of mutagenicity studies with cadmium are summarized in Tables 4-2 through 4-6. U.S. EPA (1985a) contains a thorough review of the available literature concerning cadmium mutagenicity. Results obtained in a variety of tests have been mixed. It appears that cadmium is mutagenic in some test systems under some conditions; however, the relationship between mutagenicity and carcinogenicity is not as well established for metals as for some other classes of carcinogens. McCann et al. (1975) reported that 75% of the metal carcinogens tested in the standard Ames test produced negative results.

Evaluation of lymphocytes from occupationally exposed workers has produced equivocal results and tests for chromosomal aberrations in plants have generally been positive (U.S. EPA, 1985a).

In a short-term screening test, Sanders and Mahaffey (1984) observed an increase in mammary tumors and an increase in tumors at multiple sites in male rats that were given 1-3 intratracheal instillations of cadmium oxide.

## 4.4. WEIGHT OF EVIDENCE

IARC (1982) has classified cadmium and certain cadmium compounds as Group 2B chemicals. They considered the evidence for carcinogenicity to humans to be "limited," since it is "still far from clear which were the target organs for the putative carcinogenic action of cadmium in humans."

TABLE 4-2

Mutagenicity of Cadmium: Evaluations Using Prokaryotes*

| Test Organism | Cadmium Compound | Activation | Results |
|---|---|---|---|
| Salmonella typhimurium | aqueous cadmium chloride | phenobarbitol-induced rat liver | negative |
| S. typhimurium | cadmium red in DMSO | Aroclor-induced mouse liver | negative |
| S. typhimurium | cadmium chloride | uninduced mouse liver | negative |
| S. typhimurium | cadmium diethyl-thiocarbamate in DMSO | Aroclor-induced rat liver | one dose positive, no dose response |
| Bacillus subtilis | aqueous cadmium chloride | none | weakly positive |
| B. subtilis | aqueous cadmium nitrate | none | negative |
| B. subtilis | cadmium chloride, nitrate and sulfite | none | weakly positive |

*Source: U.S. EPA, 1985a

TABLE 4-3

Mutagenicity of Cadmium: Evaluations Using Eukaryotic Cells*

| Test System | Cadmium Compound | Results |
|---|---|---|
| Saccharomyces cerevisiae | cadmium chloride | positive |
| S. cerevisiae | cadmium chloride | negative |
| Mouse lymphoma | cadmium chloride | weakly positive |
| Mouse lymphoma | cadmium sulfate | positive |
| Chinese hamster, lung | cadmium acetate, cadmium chloride | positive |
| Chinese hamster, ovary | cadmium chloride | weakly positive |
| Chinese hamster, V79 | cadmium chloride | positive |

*Source: U.S. EPA, 1985a

TABLE 4-4

Mutagenicity of Cadmium: Evaluations Using Insects*

| Organism | Test System | Compound | Results |
|---|---|---|---|
| Drosophila melanogaster | sex-linked recessive lethal | cadmium chloride | negative |
| Drosophila melanogaster | larval development sex-linked recessive lethal, sex chromosome loss | cadmium chloride | negative |
| Drosophila melanogaster | dominant lethal | cadmium chloride | positive |
| Drosophila melanogaster | sex-linked recessive lethal | cadmium stearate | negative |
| Drosophila melanogaster | sex chromosome loss | cadmium chloride | negative |
| Drosophila melanogaster | sex-linked recessive lethal | cadmium chloride | negative |
| Poekilocerus pictus | testicular meiotic chromosomes | cadmium chloride | positive |

*Source: U.S. EPA, 1985a

TABLE 4-5

Mutagenicity of Cadmium: *In vitro* Chromosome Aberrations*

| Test Cells | Cadmium Compound | Results |
|---|---|---|
| Human lymphocytes | cadmium sulfide | positive |
| Human lymphocytes | cadmium chloride | negative |
| Human lymphocytes | cadmium chloride | negative |
| WI38 and MCR5 | cadmium chloride | negative |
| Human lymphocytes ($G_0$ stage) | cadmium acetate | weakly positive |
| Chinese hamster HY cells | cadmium sulfate | positive |
| Chinese hamster CHO cells | cadmium chloride | positive with newborn calf or human serum, negative with fetal calf serum |
| Mouse mammary carcinoma, FM3A | cadmium chloride | negative |

*Source: U.S. EPA, 1985a

TABLE 4-6

Mutagenicity of Cadmium: *In vivo* Mammalian Systems*

| Organism | Endpoint | Test Compound | Results |
|---|---|---|---|
| Mouse | bone marrow cells | cadmium chloride | negative |
| Mouse | bone marrow micronuclei | cadmium chloride | negative |
| Mouse | dominant lethals | cadmium chloride | negative |
| Mouse | dominant lethal | cadmium chloride | negative |
| Mouse | postimplantation loss | cadmium chloride | negative |
| Mouse | heritable translocation | cadmium chloride | negative |
| Mouse | spermatocytes | cadmium chloride | negative |
| Mouse | oocytes | cadmium chloride | positive |
| Mouse | blastocysts | cadmium chloride | positive for aneuploidy |
| Syrian hamster | oocytes | cadmium chloride | positive |

*Source: U.S. EPA, 1985a

Evidence for carcinogenicity in animals was considered "sufficient" based upon subcutaneous and intramuscular injection studies, which were not reviewed for this document (U.S. EPA, 1980a). Evidence for activity in short-term tests was considered "inadequate" because of the conflicting results reported by various authors (see Section 4.3.).

In a more recent evaluation, U.S. EPA (1985a) classified cadmium as a Group B1 substance, probable human carcinogen, using the Agency's guidelines for carcinogen risk assessment (U.S. EPA, 1986b). This classification was based on sufficient evidence of carcinogenicity in animals and limited evidence in humans. The animal evidence included the finding of lung carcinomas in rats exposed to cadmium chloride by inhalation, and injection site and testicular tumors in rats and mice given cadmium metal or salts. The human evidence consisted of a dose-related increase in lung cancer among humans exposed to airborne cadmium that could not be explained by confounding factors. U.S. EPA (1985a) also classified cadmium in IARC Group 2A, which indicated that it is a probable human carcinogen.

While there are positive dose-response data for the inhalation and injection routes, the oral exposure experiments have not shown a response. The lack of a response following oral exposure is felt to be an issue of dosimetry (i.e., low absorption efficiency). As a result, the Carcinogen Assessment Group feels that the negative oral data are not a basis for concluding that the human potential for carcinogenicity, as implied from the weight of the evidence classification of B1, should be viewed differently for oral exposure.

## 5. REGULATORY STANDARDS AND CRITERIA

U.S. EPA (1987) calculated a 1-day HA based on a NOAEL for gastrointestinal irritation of 3 mg cadmium administered as a single oral dose to adult humans (0.043 mg/kg for a 70 kg adult) (Lauwerys et al., 1979). The 1-day HA was 0.043 mg/ℓ for a 10 kg child.

U.S. EPA (1987) also calculated 10-day HAs based on a rat NOAEL for proteinuria of 10 mg/ℓ in drinking water (0.84 mg/kg/day) that was determined in a 24-week study by Kotsonis and Klaassen (1978). However, the 10-day HA calculated from this NOAEL for a 10 kg child would be 0.08 mg/ℓ. Since this value is greater than the 1-day HA, U.S. EPA (1987) suggests that the 1-day number be used for the 10-day HA.

U.S. EPA (1987) calculated a DWEL of 0.018 mg/ℓ based on an RfD of 0.0005 mg/kg/day for a 70 kg adult consuming 2 ℓ of drinking water/day. A DWEL of 0.005 mg/ℓ was calculated using a relative source contribution from water of 25%.

WHO (1983) recommended that cadmium concentrations in drinking water be $\leq$5 µg/ℓ. NAS (1982) calculated SNARLs of 5 µg/ℓ for chronic exposure, 21 µg/ℓ for 7-day exposure and 150 µg/ℓ for 24-hour exposure. WHO (1972) proposed a provisional tolerable weekly intake of 400-500 µg (57.1-71.4 µg/day). U.S. EPA (1985b) proposed an RMCL of 0.005 mg cadmium/ℓ drinking water.

U.S. EPA (1980a) recommended an ambient water quality criterion of 10 µg/ℓ to protect against human health effects that were due to exposure to cadmium in drinking water and from eating contaminated fish and shellfish.

The ACGIH (1986) TLV for cadmium dust and salts is 0.05 mg/m³ as cadmium. The NIOSH (1976) criterion is 0.04 mg/m³. OSHA (1985) lists an 8-hour TWA-PEL and acceptable ceiling concentration for cadmium fume of 0.1 and 0.3 mg/m³, respectively. For cadmium dust, the TWA-PEL and acceptable ceiling concentrations were 0.2 and 0.6 mg/m³.

## 6. RISK ASSESSMENT

### 6.1. SUBCHRONIC REFERENCE DOSE ($RfD_S$)

6.1.1. Oral ($RfD_{SO}$). Since at present there is chronic baseline exposure of the human population (primarily through food) and since the critical effects of cadmium are dependent upon reaching a critical body burden, development of a separate subchronic estimate is not recommended.

6.1.2. Inhalation ($RfD_{SI}$). Cadmium is a metal that is a known carcinogen by the inhalation route and for which data are sufficient for computing a $q_1^*$. It is, therefore, inappropriate to calculate an inhalation RfD for cadmium.

### 6.2. REFERENCE DOSE (RfD)

6.2.1. Oral ($RfD_0$). U.S. EPA (1988b) calculated an RfD for oral exposure to waterborne cadmium based on data provided by Friberg et al. (1974). This RfD was based on a critical level of cadmium in the renal cortex of humans that is associated with renal dysfunction of 200 µg/g wet weight. Friberg et al. (1974) used a model to estimate that a daily intake of 0.352 mg cadmium/day for the first 50 years of life would result in a renal cortex level of 200 µg/g in adult humans (70 kg). Assumptions used in the model were that 4.5% of a daily oral dose was absorbed, 33% of the total body burden was in the kidneys, renal cortex concentration was 150% that of whole kidney, and that excretion amounted to 0.01% of the total body burden per day. The estimated intake of 0.352 mg/day was divided by an uncertainty factor of 10, resulting in an RfD of 0.04 mg/day for a 70 kg human, or 0.0005 mg/kg/day.

U.S. EPA (1988b) also verified an RfD for dietary exposure of 0.001 mg/kg/day by assuming that cadmium absorption from food is 2.5%. There appears to be considerable variability in cadmium uptake as a result of species differences, chemical form of the cadmium and dietary influences.

Diet composition, at least in experimental animals, appears to affect the absorption of cadmium administered either in the food or in water. Both 2.5 and 5% are within the range of reports for absorption following dietary exposure (Friberg, 1984). Data comparing uptake from food versus water in subjects consuming similar diets do not appear to be available. Both of the proposed absorption estimates appear to be reasonably conservative in the context of western diets when evaluated both in terms of the effects of dietary components on uptake, and in the context of retrospective evaluations of daily intake versus renal concentrations at autopsy. While a number of human studies have suggested absorption percentages up to 10% in humans (Friberg, 1984), there is a potential for overestimation of absorption in studies that estimate absorption based upon fecal elimination. The reason for this concern is that apparently absorption of cadmium takes place in two phases, uptake into the intestinal mucosa followed by slower and possibly incomplete absorption from the mucosa (Foulkes, 1986). Fecal elimination studies would only evaluate this first step, mucosal uptake.

6.2.2. Inhalation ($RfD_I$). Cadmium is a metal that is a known carcinogen by the inhalation route and for which data are sufficient for computing a $q_1^*$. It is, therefore, inappropriate, in the context of the guidelines for this series of documents, to calculate an inhalation RfD for cadmium.

6.3. CARCINOGENIC POTENCY ($q_1^*$)

6.3.1. Oral. Cadmium has not been shown to be carcinogenic in laboratory animals by oral administration. There are no human data (U.S. EPA, 1985a). Using the dose data for rats from Schroeder et al. (1965) and assuming a 10% upper limit of detection of tumors, U.S. EPA (1985a) estimated an upper limit for the carcinogenic potency of ingested cadmium that is 2 orders of magnitude less than for inhalation. It is possible that as a result of

extremely poor absorption from the gastrointestinal tract, cadmium is not carcinogenic when ingested; however, the negative data available can only be used to set an upper limit on potency. For these reasons, quantitative risk assessment for oral exposure to cadmium is not attempted here.

6.3.2. Inhalation. The data of Takenaka et al. (1983) for induction of lung carcinoma in rats could be used for quantitative risk assessment; however, U.S. EPA (1985a) felt that an extrapolation based on the human data for respiratory cancer (Thun et al., 1985) provided a more realistic assessment. Since this was based on an in-depth and critical review of the literature, which far exceeded the scope of the current document, this approach will be adopted here.

U.S. EPA (1985a) used a number of different approaches to derive unit risk estimates for inhalation exposure to cadmium. They suggested that if a single estimate is desired, it may be based on the maximum likelihood estimate of the linear parameter obtained from fitting the linear nonthreshold model to the Thun et al. (1985) data. This estimate for risk from a constant lifetime exposure to 1 $\mu g/m^3$ is $1.8 \times 10^{-3}$. A higher unit risk estimate of $3.5 \times 10^{-3}$ would be obtained if the 95% upper bound of the parameter estimate were used, but U.S. EPA (1985a) felt that this would introduce an unnecessary added level of conservatism because the model already overestimates the risk if nonlinear components exist or if confounding factors are present.

For purposes of comparison, U.S. EPA (1985a) also used the animal data of Takenaka et al. (1983) to derive a unit risk estimate for inhalation exposure to cadmium. They used the linearized multistage model to calculate human $q_1^*$ values of $2.1 \times 10^{-1}$ $(\mu g/kg/day)^{-1}$ for inhalation of cadmium chloride and $3.4 \times 10^{-1}$ $(\mu g/kg/day)^{-1}$ for elemental cadmium. These

values correspond to $6.0 \times 10^{-2}$ and $9.7 \times 10^{-2}$ $(\mu g/m^3)^{-1}$, respectively. The incremental unit risk from the inhalation of 1 µg of elemental cadmium/m³ of air was calculated to be $9.2 \times 10^{-2}$. Following careful consideration of all of the data, U.S. EPA (1985a) decided that the human data provided the best current basis for risk assessment. The unit risk of exposure to 1 µg/m³ based on human data, $1.8 \times 10^{-3}$, was therefore recommended by U.S. EPA (1985a). The unit risk slope is equivalent to 6.1 $(mg/kg/day)^{-1}$. This analysis has been verified by the CRAVE Workgroup and is available on IRIS (U.S. EPA, 1988a).

## 7. REFERENCES

ACGIH (American Conference of Governmental Industrial Hygienists). 1986. Threshold limit values and biological exposure indices for 1986-1987. Cincinnati, OH.

Anderson, O., J.B. Nielsen and P. Svendsen. 1986. Oral cadmium toxicology. Acta. Pharmacol. Toxicol. (Copenhagen). 59(Suppl. 7): 44-47.

Ando, M., et al. 1977. Studies on excretion and uptake of calcium by rats after continuous oral administration of cadmium. Toxicol. Appl. Pharmacol. 39: 321. (Cited in U.S. EPA, 1980a)

Armstrong, G.B. and G. Kazantzis. 1983. The mortality of cadmium workers. Lancet. 1: 1425-1427. (Cited in Oberdorster, 1986)

Armstrong, B.G. and G. Kazantzis. 1985. Prostatic cancer and chronic respiratory and renal disease in British cadmium workers: A case control study. Br. J. Ind. Med. 42: 540-545.

Baader, E.W. 1952. Chronic cadmium poisoning. Ind. Med. Surg. 21: 427. (Cited in U.S. EPA, 1980a)

Banis, R.J., et al. 1969. Dietary cadmium, iron, and zinc interactions in the growing rat. Proc. Soc. Exp. Biol. Med. 130: 802. (Cited in U.S. EPA, 1980a)

Bremner, I. 1974. Heavy metal toxicities. Q. Rev. Biophys. 7: 75-124. (Cited in U.S. EPA, 1980a)

Bunn, C.R. and G. Matrone. 1966. In vivo interactions of cadmium, copper, zinc, and iron in the mouse and rat. J. Nutr. 90: 395. (Cited in U.S. EPA, 1980a)

Buxton, R.St.J. 1956. Respiratory function in cadmium alloy casters. Br. J. Ind. Med. 13: 36. (Cited in U.S. EPA, 1980a)

Callahan, M.A., M.W. Slimak, N.W. Gabel, et al. 1979. Water-Related Environmental Fate of 129 Priority Pollutants, Vol. I. Office of Water Planning and Standards, Office of Water and Waste Management, U.S. EPA, Washington, DC. EPA 440/4.790229a.

Davies-Colley, R.J., P.O. Nelson and K.J. Williamson. 1984. Copper and cadmium uptake by estuarine sedimentary phases. Environ. Sci. Technol. 18: 491-499.

Davies-Colley, R.J., P.O. Nelson and K.J. Williamson. 1985. Sulfide control of cadmium and copper concentrations in anaerobic estuarine sediments. Mar. Chem. 16: 173-186.

Decker, L.E., R.U. Byerrum, C.F. Decker, C.A. Hoppert and R.F. Langham. 1958. Chronic toxicity studies. I. Cadmium administered in drinking water to rats. Arch. Ind. Health. 18: 228-231. (Cited in U.S. EPA, 1982)

Dixon, R.L., et al. 1976. Methods to assess reproductive effects of environmental chemicals: Studies of cadmium and boron administered orally. Environ. Health Perspect. 13: 59. (Cited in U.S. EPA, 1980a)

Elinder, C.G., et al. 1976. Cadmium in kidney cortex, liver, and pancreas from Swedish autopsies. Arch. Environ. Health. 30: 292. (Cited in U.S. EPA, 1980a)

Elinder, C.G., T. Kjellström, C. Hogstedt, K. Anderson and G. Spang. 1985. Cancer mortality of cadmium workers. Br. J. Ind. Med. 42: 651-655. (Cited in Oberdorster, 1986)

Elliott, H.A., M.R. Leberati and C.P. Huano. 1986. Competitive adsorption of heavy metals by soil. J. Environ. Qual. 15: 214-219.

Falck, F.Y., L.J. Fine, R.G. Smith, et al. 1983. Occupational exposure to cadmium and renal status. Am. J. Ind. Med. 4: 541-459.

Ferm, V.H. and S.J. Carpenter. 1967. Teratogenic effect of cadmium and its inhibition by zinc. Nature. 216: 1123. (Cited in U.S. EPA, 1980a)

Fishbein, L. 1981. Sources, transport and alterations of metal compounds: An overview. I. Arsenic, beryllium, cadmium, chromium and nickel. Environ. Health Perspect. 40: 43-64.

Fitzhugh, O.G. and F.H. Meiller. 1941. The chronic toxicity of cadmium. J. Pharm. Exp. Ther. 72: 15. (Cited in U.S. EPA, 1983)

Foulkes, E.C. 1986. Absorption of cadmium. In: Handbook of Experimental Pharmacology, E.C. Foulkes, Ed. Springer-Verlag, Berlin. Volume 80, p. 75-100.

Fox, M.R.S. and B.E. Fry. 1970. Cadmium toxicity decreased by dietary ascorbic acid supplements. Science. 169: 989.

Friberg, L. 1948a. Proteinuria and kidney injury among workers exposed to cadmium and nickel dust. J. Ind. Hyg. 30: 32-36. (Cited in U.S. EPA, 1980a)

Friberg, L. 1948b. Proteinuria and kidney injury among workers exposed to cadmium and nickel dust in a storage battery plant. Proc. Int. Congr. Ind. Med. 9: 641. (Cited in U.S. EPA, 1980a)

Friberg, L. 1950. Health hazards in the manufacture of alkaline accumulators with special reference to chronic cadmium poisoning -- A clinical and experimental study. Acta Med. Scand. 138 Supplement CCXL. (Cited in U.S. EPA, 1980a)

Friberg, L., M. Piscator, G.F. Nordberg and T. Kjellstrom. 1974. Cadmium in the Environment, 2nd ed. CRC Press, Cleveland, OH. (Cited in U.S. EPA, 1980a)

Gerritse, R.G. and W. Van Driel. 1984. The relationship between adsorption of trace metals, organic matter and pH in temperate soils. J. Environ. Qual. 13: 197-204.

Gunn, S.A., T.C. Gould and W.A.D. Anderson. 1963a. Cadmium-induced interstitial cell tumors in rats and mice and their prevention by zinc. J. Natl. Cancer Inst. 31: 745-759. (Cited in U.S. EPA, 1980a)

Gunn, S.A., T.C. Gould and W.A.D. Anderson. 1963b. The selective injurious response of testicular and epididymal blood vessels to cadmium and its prevention by zinc. Am. J. Pathol. 42: 685-693. (Cited in U.S. EPA, 1980a)

Gunn, S.A., et al. 1964. Effect of zinc on carcinogenesis by cadmium. Proc. Soc. Exp. Biol. Med. 115: 653. (Cited in U.S. EPA, 1980a)

Hill, C.H., G. Matrone, W.L. Payne and C.W. Barber. 1963. In vivo interactions of cadmium with copper, zinc, and iron. J. Nutr. 80: 227-235. (Cited in U.S. EPA, 1980a)

Holden, H. 1965. Cadmium fume. Ann. Occup. Hyg. 8: 51-54. (Cited in U.S. EPA, 1980a)

Holden, H. 1980. Further mortality studies on workers exposed to cadmium fumes. Presented at the Seminar on Occupational Exposure to Cadmium, London. (Cited in Oberdorster, 1986)

Hollander, M.L. and S.C. Carapella, Jr. 1978. Cadmium and cadmium alloys. In: Kirk-Othmer Encyclopedia of Chemical Technology, 3rd ed., Vol. 4. M. Grayson and D. Eckroth, Ed. John Wiley and Sons, Inc., NY. p. 387-396.

Humperdinck, K. 1968. Kadmium und Lungenkrebs. Med. Klin. 63: 948-951. (Cited in Oberdorster, 1986)

IARC (International Agency for Research on Cancer). 1976. Cadmium and compounds. In: Cadmium, Nickel, Some Epoxides, Miscellaneous Industrial Chemicals, and General Considerations on Volatile Anaesthetics. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man. IARC, WHO, Lyons, France. Vol. 11, p. 39-76. (Cited in U.S. EPA, 1983)

IARC (International Agency for Research on Cancer). 1982. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Chemicals, Industrial Processes and Industries Associated with Cancer in Humans. IARC Monographs Supplement 4. WHO, Lyons, France. p. 71-73.

Kajikawa, K., I. Nakanishi and K. Kuroda. 1981. Morphological changes of the kidney and bone of rats in chronic cadmium poisoning. Exp. Molec. Pathol. 34: 9-24. (Cited in U.S. EPA, 1983)

Kanisawa, M. and H.A. Schroeder. 1969. Life term studies on the effect of trace elements on spontaneous tumors in mice and rats. Cancer Res. 29: 892-895. (Cited in U.S. EPA, 1982)

Kazantzis, G., et al. 1963. Renal tubular malfunction and pulmonary emphysema in cadmium pigment workers. Q. J. Med. New Series. 32: 165. (Cited in U.S. EPA, 1980a)

Kipling, M.D. and J.A.H. Waterhouse. 1967. Cadmium and prostatic carcinoma. Lancet. 1: 730-731. (Cited in Oberdorster, 1986)

Kjellström, T., L. Friberg and B. Rahnster. 1979. Mortality and cancer morbidity among cadmium-exposed workers. Environ. Health Perspect. 28: 199-204. (Cited in Oberdorster, 1986)

Kjellstrom, T., C.G. Elinder and L. Friberg. 1984. Conceptual problems in establishing the critical concentration of cadmium in human kidney cortex. Environ. Res. 33: 284-295. (Cited in U.S. EPA, 1985b)

Kobayashi, J. 1970. Relation between the "itai-itai" disease and the pollution of river water by cadmium from a mine. Proc. Int. Water Pollut. Res. Conf. I-25/1-7. (Cited in U.S. EPA, 1980a)

Kolakowski, J., B. Baranski and B. Opalska. 1983. Effect of long-term inhalation exposure to cadmium oxide fumes on cardiac muscle ultrastructure in rats. Toxicol. Lett. 19: 273-278.

Koller, L.D., J.H. Exon and J.G. Roan. 1975. Antibody suppression by cadmium. Arch. Environ. Health. 30: 598-601.

Kotsonis, F.N. and C.D. Klaassen. 1978. The relationship of metallothionein to the toxicity of cadmium after prolonged oral administration to rats. Toxicol. Appl. Pharmacol. 46: 39-54. (Cited in U.S. EPA, 1985b)

Krasovskii, G.N., et al. 1976. Toxic and gonadotropic effects of cadmium and boron relative to standards for these substances in drinking water. Environ. Health Perspect. 13: 69. (Cited in U.S. EPA, 1980a)

Lane, R.E. and A.C.P. Campbell. 1954. Fatal emphysema in two men making a copper cadmium alloy. Br. J. Ind. Med. 11: 118. (Cited in U.S. EPA, 1980a)

Lauwerys, R., J.P. Buchet, H.A. Roels, J. Brouwers and D. Stanescu. 1974. Epidemiological survey of workers exposed to cadmium -- Effect on lung, kidney, and several biologic indices. Arch. Environ. Health. 28: 145-148. (Cited in U.S. EPA, 1980a, 1983)

Lauwerys, R.R., H. Roels, M. Regniers, N.P. Buchet, A. Bernard and A. Goret. 1979. Significance of cadmium concentration in blood and urine in workers exposed to cadmium. Environ. Res. 20: 375-391. (Cited in U.S. EPA, 1985b)

Lemen, R.A., J.S. Lee, J.K. Wagoner and H.P. Blejer. 1976. Cancer mortality among cadmium production workers. Ann. NY Acad. Sci. 271: 273-279. (Cited in Oberdorster, 1986)

Levy, L.S. and J. Clark. 1975. Further studies on the effect of cadmium on the prostate gland. I. Absence of prostatic changes in rats given oral cadmium sulphate for two years. Ann. Occup. Hyg. 17: 205-211. (Cited in IARC, 1976; U.S. EPA, 1982)

Levy, L.S., J. Clark and F.J.C. Roe. 1975. Further studies on the effect of cadmium on the prostate gland. II. Absence of prostatic changes in mice given oral cadmium sulphate for eighteen months. Ann. Occup. Hyg. 17: 213-220. (Cited in IARC, 1976; U.S. EPA, 1982)

Lewis, G.P., H. Lyle and S. Miller. 1969. Association between elevated hepatic water-soluble protein-bound cadmium levels and chronic bronchitis and/or emphysema. Lancet. 2: 1330-1333. (Cited in U.S. EPA, 1980a)

Lewis, T.R., et al. 1977. Test of suitability of TLV for CdO fume. Unpublished results. Experimental Toxicology Branch, NIOSH, Cincinnati, OH. (Cited in Stokinger, 1981)

Loser, E. 1980. A 2-year oral carcinogenicity study with cadmium in rats. Cancer Lett. 9(3): 191-198. (Cited in U.S. EPA, 1982)

Lykins, B.W., Jr. and J.M. Smith. 1976. Interim Report on the Impact of Public Law 92-500 on Municipal Pollution Control Technology. EPA 600/2-76-018. (Cited in U.S. EPA, 1980a)

McCann, J., E. Choi, E. Yamasaki and B.N. Ames. 1975. Detection of carcinogens as mutagens in the Salmonella/microsome test: Assay of 300 chemicals. Proc. Natl. Acad. Sci. 72: 5135-5139. (Cited in U.S. EPA, 1980a)

McLellan, J.S., et al. 1978. Measurement of dietary cadmium in humans. J. Toxicol. Environ. Health. 4: 131. (Cited in U.S. EPA, 1980a)

Muramatsu, S. 1974. Research about cadmium-pollution in the Kakehashi River basin. Jap. J. Pub. Health. 21: 299. (Cited in U.S. EPA, 1980a)

NAS (National Academy of Sciences). 1982. Drinking Water and Health. NAS, Washington, DC. p. 939. (Cited in U.S. EPA, 1985b)

NIOSH (National Institute for Occupational Safety and Health). 1976. Criteria for a Recommended Standard...Occupational Exposure to Cadmium. U.S. DHEW, PHS, CDC, Rockville, MD. Publ. No. 76-192. (Cited in U.S. EPA, 1980a, 1983)

Nogawa, K., et al. 1978. Statistical observations of the dose-response relationships of cadmium based on epidemiological studies in the Kakehashi River basin. Environ. Res. 15: 185. (Cited in U.S. EPA, 1980a)

Oberdorster, G. 1986. Airborne cadmium and carcinogenesis of the respiratory tract. Scand. J. Work Environ. Health. 12: 523-537.

OSHA (Occupational Safety and Health Administration). 1985. OSHA Occupational Standards. Permissible Exposure Limits. 29 CFR 1910.1000.

Parizek, J. 1957. The destructive effect of cadmium ion on testicular tissue and its prevention by zinc. J. Endocrin. 15: 56. (Cited in U.S. EPA, 1980a)

Parizek, J., et al. 1969. Metabolic interrelationships of trace elements. Effects of zinc salts on the survival of rats intoxicated with cadmium. Physiologia Bohemoslov. 18: 89. (Cited in U.S. EPA, 1980a)

Paterson, J.C. 1947. Studies on the toxicity of inhaled cadmium. III. The pathology of cadmium smoke poisoning in man and in experimental animals. J. Ind. Hyg. Toxicol. 29: 294. (Cited in U.S. EPA, 1980a, 1982)

Piscator, M. 1981. Role of cadmium in carcinogenesis with special reference to cancer of the prostate. Environ. Health Perspect. 40: 107-120.

Potts, C.L. 1965. Cadmium proteinuria -- The health of battery workers exposed to cadmium oxide dust. Ann. Occup. Hyg. 8: 55-61. (Cited in U.S. EPA, 1980a)

Rahola, T., et al. 1973. Retention and elimination of $^{155}\mu$Cd in man. In: Health Physics Problems of Internal Contamination. Akademiai Kiado, Budapest. (Cited in U.S. EPA, 1980a)

Roels, R., R. Lauwerys and A.N. Dardenne. 1983. The critical level of cadmium in human renal cortex: A reevaluation. Toxicol. Lett. 15: 357-360. (Cited in U.S. EPA, 1985b)

Sanders, C.L. and J.A. Mahaffey. 1984. Carcinogenicity of single and multiple intratracheal instillations of cadmium oxide in the rat. Environ. Res. 33: 227-233. (Cited in U.S. EPA, 1985a)

Sato, K. 1977. Peripheral nerve lesions and carcinogenesis after long-term administration of cadmium in the rat. Kumamoto Med. J. 51(4): 242-264. (Cited in U.S. EPA, 1982)

Schroeder, H.A. and M. Mitchener. 1971. Toxic effects of trace elements on the reproduction of mice and rats. Arch. Environ. Health. 23: 102-106. (Cited in U.S. EPA, 1980a, 1983)

Schroeder, H.A., W.H. Vinton and J.J. Balassa. 1963. Effects of chromium, cadmium, and lead on the growth and survival of rats. J. Nutr. 80: 48-54. (Cited in U.S. EPA, 1983)

Schroeder, H.A., J.J. Balassa and W.H. Vinton, Jr. 1964. Chromium, lead, cadmium, nickel and titanium in mice: Effect on mortality, tumors and tissue levels. J. Nutr. 83: 239-250. (Cited in U.S. EPA, 1982, 1983)

Schroeder, H.A., J.J. Balassa and W.H. Vinton, Jr. 1965. Chromium, cadmium and lead in rats: Effects on lifespan, tumors and tissue levels. J. Nutr. 86: 51-66. (Cited in U.S. EPA, 1982, 1983)

Smith, J.P., J.C. Smith and A.J. McCall. 1960. Chronic poisoning from cadmium fumes. J. Path. Bact. 80: 287-296. (Cited in U.S. EPA, 1980a)

Smith, T.J., et al. 1976. Pulmonary effects of chronic exposure to airborne cadmium. Am. Rev. Resp. Dis. 114: 161. (Cited in U.S. EPA, 1980a)

Snider, G.G., et al. 1973. Centrilobular emphysema experimentally induced by cadmium chloride aerosol. Am. Rev. Resp. Dis. 108: 40. (Cited in U.S. EPA, 1980a)

Sorahan, T. and J.A. Waterhouse. 1983. Mortality study of nickel-cadmium battery workers by the method of regression models in life tables. Br. J. Ind. Med. 4: 293-300. (Cited in Oberdorster, 1986)

Starcher, B.C. 1969. Studies on the mechanism of copper absorption in the chick. J. Nutr. 97: 321-326. (Cited in U.S. EPA, 1980a)

Stokinger, H.E. 1981. Cadmium. In: Patty's Industrial Hygiene and Toxicology, Vol. 2A, 3rd ed., G.D. Clayton and F.E. Clayton, Ed. John Wiley and Sons, Inc., New York. p. 1563-1583.

Suzuki, S., et al. 1969. Dietary factors influencing upon retention rate of orally administered $^{109}CdCl_2$ in mice with special reference to calcium and protein concentrations in diet. Ind. Health. 7: 155. (Cited in U.S. EPA, 1980a)

Takenaka, S., H. Oldiges, H. Konig, D. Hochrainer and G. Oberdorster. 1983. Carcinogenicity of cadmium aerosols in Wistar rats. J. Natl. Cancer Inst. 70: 367-373.

Thun, M.J., T.M. Schnorr, A.B. Smith, W.E. Halperin and R.A. Lemen. 1985. Mortality among a cohort of U.S. cadmium production workers -- An update. J. Natl. Cancer Inst. 74(2): 325-333.

Tsuchiya, K. 1967. Proteinuria of workers exposed to cadmium fume -- The relationship to concentration in the working environment. Arch. Environ. Health. 14: 875-880. (Cited in NIOSH, 1976; U.S. EPA, 1983)

U.S. EPA. 1975. Scientific and technical assessment report on cadmium. National Environmental Research Center, Research Triangle Park, NC. EPA 600/6-75-003. (Cited in U.S. EPA, 1980a)

U.S. EPA. 1980a. Ambient Water Quality Criteria for Cadmium. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Water Regulations and Standards, Washington, DC. EPA 440/5-80-025. NTIS PB 81-117368.

U.S. EPA. 1980b. Guidelines and Methodology Used in the Preparation of Health Effects Assessment Chapters of the Ambient Water Quality Criteria Documents. Federal Register. 45: 79347-79357.

U.S. EPA. 1982. Review of Toxicologic Data in Support of Evaluation for Carcinogenic Potential of Cadmium and Compounds. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste and Emergency Response, Washington, DC.

U.S. EPA. 1983. Reportable Quantity for Cadmium (and Compounds). Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste and Emergency Response, Washington, DC.

U.S. EPA. 1984. Methodology and Guidelines for Reportable Quantity Determinations Based on Chronic Toxicity Data. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste and Emergency Response, Washington, DC.

U.S. EPA. 1985a. Updated mutagenicity and carcinogenicity assessment of cadmium. Prepared by the Office of Health and Environmental Assessment, Carcinogen Assessment Group, Washington, DC. NTIS PB 85-243533.

U.S. EPA. 1985b. National Primary Drinking Water Regulations; Synthetic Organic Chemicals, Inorganic Chemicals and Microorganisms. Federal Register. 50(219): 46936-47022.

U.S. EPA. 1986a. Reference Values for Risk Assessment. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria Assessment Office, Cincinnati, OH for the Office of Solid Waste, Washington, DC.

U.S. EPA. 1986b. Guidelines for Carcinogen Risk Assessment. Federal Register. 51(185): 33992-34003.

U.S. EPA. 1987. Health Advisory for Cadmium. March 31, 1987. Prepared by the Office of Drinking Water, Washington, DC. Final.

U.S. EPA. 1988a. Integrated Risk Information System. Risk Estimate for Carcinogens for Cadmium. On-line. (Revised; verification date 03/01/88). Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH.

U.S. EPA. 1988b. Integrated Risk Information System (IRIS). Reference Dose (RfD) for Oral Exposure for Cadmium. On-line. (Verification date 05/25/88). Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH.

Washko, P.W. and R.J. Cousins. 1976. Metabolism of $^{109}Cd$ in rats fed normal and low-calcium diets. J. Toxicol. Environ. Health. 1: 1055. (Cited in U.S. EPA, 1980a)

Weast, R.C. 1985. CRC Handbook of Chemistry and Physics, 66th ed. CRC Press, Inc., Raton, FL. p. B80-B81.

White, L.D., M.O. Varner, C.H. Hine, F. Crookston and R.B. Watson. 1985. An epidemiological study of cadmium exposed workers. In: Abstr. American Industrial Hygiene Conference, Las Vegas, May 19-24. American Industrial Hygiene Association, Cincinatti, OH. 179 p. (Cited in Oberdorster, 1986)

WHO (World Health Organization.) 1972. Evaluation of certain food additives and the contaminants mercury, lead and cadmium. Sixteenth Report of the Joint FAO/WHO Expert Committee on Food Additives. Geneva, Switzerland: WHO Technical Report Series No. 505, FAO Nutrition Meetings Report Series No. 51. (Cited in U.S. EPA, 1985a)

WHO (World Health Organization) Task Group. 1977. Environmental health aspects of cadmium. WHO, Geneva. (Cited in U.S. EPA, 1980a)

WHO (World Health Organization). 1983. Guidelines for drinking water quality - recommendations. Volume 1. Draft. WHO, Geneva. (Cited in U.S. EPA, 1985b)

Worker, N.A. and B.B. Migicovsky. 1961. Effect of vitamin D on the utilization of zinc, cadmium and mercury in the chick. J. Nutr. 75: 222. (Cited in U.S. EPA, 1980b)

Yuhas, E.M., T.S. Miya and R.C. Schnell. 1979. Dose-related alterations in growth and mineral disposition by chronic oral cadmium administration in the male rat. Toxicology. 12: 19-29. (Cited in U.S. EPA, 1983)

00384

## APPENDIX

### Summary Table for Cadmium

| | Species | Dose/Exposure | Effect | Reference Dose (RfD or $RfD_S$) | Reference |
|---|---|---|---|---|---|
| **NONCARCINOGENIC EFFECTS** | | | | | |
| Oral | | | | | |
| $RfD_{SO}$ | NA | NA | NA | ND | NA |
| $RfD_O$ | human | 0.352 mg/day | renal dysfunction | 5E-4 mg/kg/day (waterborne)<br>1E-3 mg/kg/day (dietary) | Friberg et al., 1974; U.S. EPA, 1988b |
| **CARCINOGENIC EFFECTS** | | | | | |
| Inhalation | human | occupational | lung cancer | Unit Risk Slope: 6.1 $(mg/kg/day)^{-1}$ | Thun et al., 1985; U.S. EPA, 1985a |

NA = Not applicable; ND = not derived



08/15/88